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| 09/379,308      | 08/23/1999  | PHILIPPE DIAZ        | 016800-318          | 1123             |

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| EXAMINER |
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LUKTON, DAVID

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| ART UNIT | PAPER NUMBER |
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1653

DATE MAILED: 08/21/2003

26

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/379,308

Applicant(s)

DIAZ ET AL.

Examiner

David Lukton

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 19 June 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 60-74 and 80-109 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 60-74 and 80-109 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s) \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

Pursuant to the directives of paper No. 25 (filed 6/19/03) claims 60, 65, 70, 80, 85, 90, 95, 100 have been amended, claims 75-79 have been cancelled, and claims 105-109 added.

Claims 60-74, 80-109 are pending.

Applicants' arguments filed 6/19/03 have been considered and found persuasive in part. The rejection of claims 60-104 under 35 U.S.C. §112 second paragraph is withdrawn. However, claims 60-74, 80-109 are rejected under 35 U.S.C. 112, first paragraph.

※

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60-74, 80-109 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Arguments in support of this ground of rejection were provided in the previous Office action (mailed 12/19/02).

In the response filed 6/19/03, the last argument made (page 98, paper No. 25) is that, although this rejection has been imposed under 35 U.S.C. §112, first paragraph, it is really

a rejection under 35 USC §101. It is asserted (response, 6/19/03) that the examiner has characterized the claimed methods as "lack[ing] credible use". However, in the Office action mailed 12/19/02, there was no rejection under 35 USC §101, and no assertion by the examiner that the claimed methods lack a credible use. Accordingly, this particular argument is moot.

In the response filed 6/19/03, it is argued that the specification provides methods of making the compounds to which the claims are drawn. However, the examiner has not argued that "undue experimentation" would be required to synthesize any one of the compounds. It is also argued (response filed 6/19/03) that "the specification provides ...methods of using the compounds...[and] formulations ... to treat specific conditions (see examples)". However, the fundamental point is that the specification does not teach the skilled artisan how to use the compounds to treat the diseases that are recited in the claims. What the specification does provide is speculation as to how one could try to use the compounds. It is true that on pages 76-83 (specification) there are suggestions about how one could combine the compounds (to which the claims are drawn) with various carriers that are known to the drug formulation specialist of ordinary skill. However, any organic compound can be combined with a pharmaceutically acceptable carrier. But combining a therapeutically ineffective compound with an inactive carrier does not give rise to a composition that can be used to treat any of the diseases that are recited in the claims.

It is also argued (response filed 6/19/03) that the declaration filed 9/18/00 (paper No. 11) provides enablement for the claimed invention. First, the declaration makes reference to Bailly (*Skin Pharmacol* 3, 256, 1990). This reference discloses experiments in which various compounds were tested for their propensity to induce secretion of plasminogen activator (PA) in F9 murine embryonal carcinoma cells. The reference also states that the induction of PA secretion correlates with morphological changes occurring in treated embryonal carcinoma cells, and provides a means to monitor F9 differentiation. The authors of the article applied the label "retinoid" to the tested compounds. Also stated (p. 264) is that (a) it is not known which RA receptors are involved in the induction of PA in F9 cells, (b) the mechanism of PA induction by retinoids has not been elucidated, and (c) the capacity of each retinoid to induce a biological response... is not related to either the AC<sub>50</sub> parameter or to receptor affinity. Next, the declaration argues that, using assays described in Levin (*Nature* 355 359, 1992) and in Allenby (*Proc. Natl. Acad. Sci.* 90, 30, 1993), two of the compounds of the claims were tested for RXR binding, "RXR transactivation", and "RXR transactivation AC". It is not clear what is meant by "RXR transactivation", and "RXR transactivation AC"; perhaps declarant prepared a CRBP<sub>II</sub>-RXRE-CAT reporter plasmid, and perhaps not. It is also not clear exactly what "RXR binding" refers to; Levin makes reference to three subtypes of RAR receptors, i.e., RAR $\alpha$ , RAR $\beta$ , RAR $\gamma$ . It remains an open question as to the receptor subtypes that may be referenced by the term

"RXR binding". Perhaps it is RXR $\alpha$ , or perhaps it is some undetermined mixture of subtypes; the declaration does not address this issue. Next, the declaration points to Safonova (*Biochem Biophys Res Commun* 204, 498, 1994), and argues that this reference discloses the usage of "such agonists" on cell differentiation and potential therapeutic utility. This reference discloses that a compound to which the label "retinoid" has been applied stimulated glycerol-3-phosphate dehydrogenase activity, and that the compound "CD367" stimulated expression of RAR $\alpha$ , RAR $\beta$ , and RAR $\gamma$ . It is not clear that the "such agonists" disclosed in Safonova are the same as the "such agonists" disclosed in Bailly, Allenby or Levin, but even if they are, Safonova does not assert that any of the compounds which stimulate glycerol-3-phosphate dehydrogenase activity, or which stimulate expression of RAR $\alpha$ , RAR $\beta$ , and RAR $\gamma$  can be used to treat even one of the disorders recited in instant claims 60-74 or 80-109.

Next, the declaration has pointed to Hong (*Retinoids and Human Cancer*, 1994). No pages numbers are given. However, the copy of pages 598-623 does not show that there is even one compound which exhibits any of the *in vitro* activities described in Bailly, Allenby or Levin, nor is there an assertion that there exists a compound which exhibits any of the *in vitro* activities described in Bailly, Allenby or Levin, and at the same time can be used to treat any of the disorders recited in instant claims 60-74 or 80-109. It may be the case that some therapeutic utility exists for vitamin A itself, but none of the claims is drawn

to a therapeutic use of vitamin A.

Next, the declaration has pointed to Lippman and DiGiovanna (*Retinoids in Skin Cancer*). Again, no page numbers were indicated. However, the copy of pages 179-196 (provided by applicants) was considered. The reference does discuss experiments with 13-cis retinoic acid (isotretinoin); it may well be the case that this particular agent is efficacious in the treatment of one or more dermatological disorders; but again, there is no connection between the *in vitro* data of the declaration, or that of Bailly, Allenby or Levin (on the one hand), and an attribution of the pharmacological effects of 13-cis retinoic acid to applicants' *in vitro* data (on the other hand).

Next, the declaration has pointed to Kavanagh (*Retinoids and Cervical Cancer*). Again, no page numbers were specified. However, pages 271-280 were considered. It is true that the authors have suggested some efficacy of all-*trans*-retinoic acid in the treatment of cervical dysplasia, and possibly some benefit following administration of 13-cis retinoic acid to patients with invasive cervical cancer. But again, it is not apparent that (a) there is a property shared by both retinoic acid and applicants' compounds that is manifest in an *in vitro* biochemical assay, and (b) that the presence or absence of this property which is so manifest correlates with the efficacy of compounds in therapeutic applications.

Next, the declaration has pointed to Meyskens (*J. Am. Acad. Dermatol.* **15**, 822, 1986). The authors do indicate that some histological changes in patients afflicted with dysplastic

nevus syndrome occurred following topical administration of tretinoin. Again, no connection is drawn between applicants' *in vitro* assays, and treatment of dysplastic nevus syndrome.

Next, it is argued that the compound of example 2 (specification) augments ear oedema in an unidentified organism. The means by which the ear oedema in this unidentified organism has been induced has not been specified. In addition, there are no claims drawn to a method of exacerbating the condition of a patient suffering from an ear oedema. Furthermore, there is no reference identified in the response filed 6/19/03 (or any previous response) which endeavors to show a correlation between the propensity of a compound to exacerbate ear oedema, and the efficacy of that compound in the treatment of any of the disorders recited in claims 60-74, 80-109.

Next, it is argued (response filed 6/19/03) that the level of skill in the field of retinoid research is high. Perhaps this is true, but if a highly skilled researcher endeavors to treat a patient suffering from, e.g., a proliferative or inflammatory disorder using a compound which is therapeutically ineffective, no amount of skill will cause the patient's condition to improve. Next, it is argued (response filed 6/19/03) that "research and treatment methods are well known". Certainly, there is a considerable body of literature which describes experiments which have been carried out to assess therapeutic efficacy of compounds. Further, various compounds do exist which have been shown to be effective



in the treatment of some kinds of cancer and inflammation. Of these compounds, there may be a few that exhibit one or more *in vitro* effects exhibited by 13-cis, or *all trans*-retinoic acid. But neither the response filed 6/19/03, nor the declaration filed 9/18/00 (paper No. 11) explains what *in vitro test* of retinoic acid (or any other compound) is predictive of therapeutic efficacy. In addition, no evidence is presented that there exists a given *in vitro* test which predicts therapeutic efficacy. In addition, no evidence has been provided as to what criteria the skilled artisan believes are necessary for a compound to exhibit in order to qualify as a "retinoid", and no evidence has been provided as to what criteria the skilled artisan believes are sufficient for a compound to exhibit in order to qualify as a "retinoid". But even if one stipulates, for the sake of argument, that the compounds (to which the claims are drawn) qualify, by one criterion or another, as "retinoids", the reality is that, where retinoids are concerned, one cannot "predict" therapeutic efficacy. It is not the case that all retinoids exhibit the same activities, either *in vitro* or *in vivo*, and moreover, many retinoids are in fact ineffective in treatment of various proliferative disorders. Consider the following references, and their teachings:

- Benedetti (*Blood* 87 (5) 1939-50, 1996) discloses that "RAR- and RAR *alpha*-selective retinoids were able to induce growth arrest, granulocytic differentiation, and type II TGase, whereas the RXR-selective retinoid SR11217 was inactive". The current and previous responses have asserted that the compounds of examples 2 and 4 function as RXR agonists. This reference supports the proposition that RXR-selective retinoids can be inactive.
- Byers S (*Endocrinology* 137 (8) 3265-73, 1996) discloses that "A retinoid X

receptor-specific ligand was ineffective". This reference supports the proposition that RXR-selective retinoids can be inactive.

- Chandraratna R A (*Journal of the American Academy of Dermatology* 37 (2 Pt 3), S12-S17, 1997) discloses that tazarotene selectively transactivates RAR *beta* and RAR *gamma* subtypes and is inactive at retinoid X receptors (RXRs). This reference is cited to merely reinforce the fact that there is a distinction between RAR's and RXR's and that compounds to which the term "retinoid" is applied would have to be divided, at a bear minimum, into at least two separate categories; what may be true of one is not necessarily going to be true of the other.
- Chen S et al., (*Journal of Pharmacy and Pharmacology* 47 (8) 626-31, 1995) discloses that "BMS-181163 (4-acetamidophenyl retinoate, previously reported as BMY-30123), the acetamidophenyl ester of all-trans-retinoic acid (tRA), is ... ineffective for the treatment of acne in patients." Thus, a compound to which the label "retinoid" has been applied is ineffective in the treatment of at least one skin disorder.
- Dockx P. (*British Journal of Dermatology* 133 (3) 426-32, 1995) discloses that "retinoids derived from retinol or beta-carotene are inactivated, among other ways, by enzymes belonging to the P450 cytochrome group". This reference illustrates one of the pitfalls in attempting to extrapolate from *in vitro* experiments to *in vivo* therapies. The disclosed compounds (to which the claims are drawn) could very well be inactivated by one or more P-450 isozymes. The term cytochrome P-450 refers not to a single enzyme, but rather a group of hundreds of thousands, if not millions of isozymes. Moreover, the isozymes are induced in response to xenobiotics, and the particular isozymes which may be induced cannot be predicted from the structure of the compound.
- Elder J T et al., (*Journal of Investigative Dermatology* 106 (3) 517-21, 1996) discloses (page 519) that binding affinity for RAR receptors does not correlate with *in vivo* assays or other *in vitro* assays.
- Kinoshita et al. (*Blood*, 95 (9) 2821-8, 2000) discloses results of *in vitro* assays conducted on a series of retinoids. At least one of the RXR-selective agonists was inactive. This reference is cited to reinforce the examiner's position that "retinoids" do not constitute a monolithic entity; compounds belonging to this group span a diverse spectrum of *in vitro* activities. Accordingly, attempting to extrapolate from

the activities of one "retinoid" to another constitutes a tenuous proposition.

- Miller W. H. et al., (*Blood* **85** (11) 3021-7, 1995) discloses results of a study of treatment of patients afflicted with leukemia. Miller reports that despite achieving favorable results *in vitro*, only one patient in seven achieved remission. This reference supports the assertion of "unpredictability" in the extrapolation from *in vitro* data to a therapeutic intervention.
- Muccio D. et al. (*J. Med Chem.* **41** (10) 1679-87, 1998) discloses that at least one compound was effective at binding to RAR, but was not effective at activating RAR. This supports the assertion that mere binding to a receptor is not a reliable indicator of activity. In addition, data presented (e.g., table 3) supports the contention that retinoid/receptor interactions are very specific, very exacting, and above all, very unpredictable.
- Paraskevaidis A et al. (*Dermatology* **196** (1) 171-5, 1998) discloses that "...the biological efficacy of ... retinoids could be greatly impaired by their rapid metabolism to inactive compounds"
- Sakaue et al. (*Molecular Pharmacology* **55** (4) 668-76, 1999) discloses (e.g., page 673) that AHPN, although a retinoid, does not exhibit growth arrest and apoptosis via the RAR or RXR receptor. This brings up the point that the biological activities of "retinoids" do not necessarily correlate with their ability to interact with retinoid receptors. Accordingly, extrapolation from studies on RAR or RXR is "unpredictable". Moreover, the compound AHPN, although a retinoid, behaved differently from retinoic acid in various assays.
- Shiohara M et al. (*Blood* **93** (6) 2057-66, 1999) discloses that SR11363 (Retinoid B) was inactive in a cell assay, even though this compound selectively activated RAR-*beta* and *gamma*.
- Sun S Y et al. (*Cancer Research* **57** (21) 4931-9, 1997) discloses that several RXR selective retinoids were inactive in a carcinoma cell assay. This supports the assertion that assays based only on interaction with the RXR receptor are unreliable indicators of activity in proliferative disorders.
- Tashima T et al (*Chemical and Pharmaceutical Bulletin* **45** (11) 1805-13, 1997) presents data on various retinoids, a few of which were inactive. This reference

supports the proposition that structure/activity relationships *in vitro* are unpredictable.

- Tockman, (*IARC Scientific Publications* 154 257-70, 2001) discloses that in trials with lung cancer end-points, administration of retinoids either was ineffective or, in the case of beta-carotene, led to greater lung cancer incidence and mortality. The reference also supports the proposition that extrapolating from animal models to humans is unpredictable.
- Wan H et al., (*Cancer Research* 61 (2) 556-64, 2001) discloses that "nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs)... mediate most of the effects of retinoids on cell growth and differentiation. Despite expressing abundant levels of RAR *beta* mRNA, lung adenocarcinoma H1792 cells are resistant to the growth-inhibitory effects of all-trans-retinoic acid...". Thus, studies of interactions between retinoids are not necessarily a reliable indicator of *in vivo* activity.
- Weinstein G. D., et al. (*Journal of the American Academy of Dermatology* 37 (1) 85-92, 1997) discloses that "Previous topical retinoids have generally been either ineffective or too irritating for therapy of psoriasis". Thus, this reference teaches that there exist compounds to which the label "retinoid" has been applied, and yet which are not effective in the treatment of psoriasis.

Thus, the foregoing conclusions may be drawn from the references cited by the examiner:

- (a) "retinoids" do not constitute a monolithic entity; what may be true for one retinoid in an *in vitro* assay is not necessarily true for another. Similarly, what may be true for one retinoid in an *in vivo* assay is not necessarily true for another. (b) structure/activity relationships *in vitro* are unpredictable; (c) several retinoids are known in the art to be ineffective in the treatment of various proliferative and skin disorders; (d) some compounds which have been termed "retinoids" may exert their effects by mechanisms which are independent of the RAR and RXR receptors; (e) retinoids are often inactivated by

cytochrome P-450 *in vivo*, and the extent of that inactivation is unpredictable.

In response to the teachings of the foregoing references (Benedetti, Byers, Chandraratna, Chen, Dockx, Elder, Kinoshita, Miller, Muccio, Paraskevaidis, Sakaue, Shiohara, Sun, Tashima, Tockman, Wan, Weinstein) it is argued (response filed 6/19/03) that applicants do not bear any burden to comment on the teachings of these references until such time as the examiner explains how the references support the §112, first paragraph rejection. Such explanation has been provided in this, and the prior Office action. Applicant has not addressed the criteria that are necessary or sufficient for a compound to qualify as a "retinoid". But if it is true that the disclosed compounds are "retinoids", the question becomes, can the skilled artisan "predict" therapeutic efficacy based on the assumption that a compound is a retinoid? The cited references provide numerous examples of compounds which have been termed "retinoids" by skilled artisans, yet which compounds, at the same time, are therapeutically ineffective at treating one or more of the disorders recited in the claims. The premise of the response filed 6/19/03 (and previous responses) is that when the term "retinoid" is applied to a compound, the skilled artisan can "predict" therapeutic efficacy in the treatment of cancer, inflammation, and other disorders (recited in claims 60-74, 80-109). This is unpersuasive. The cited references demonstrate that such a prediction based upon the application of the "retinoid" label will, more likely than not, fail. Thus, if it is true that the quality or state of being a "retinoid" is the nexus

required for the skilled artisan to assess therapeutic efficacy, the cited references firmly support the conclusion of unpredictability in the treatment of cancer, inflammation, and the other disorders recited in the claims.

In addition to the foregoing, the specification provides no guidance as to how to use the claimed compounds to treat the recited diseases, apart from an invitation for others to experiment. There are no working examples which show the skilled artisan how to use the disclosed compounds to treat the recited disorders. The prior art provides no suggestion that the compounds (to which the claims are drawn) can be used to treat human disease. Finally, the evidence shows that when a skilled artisan endeavors to treat human disease using retinoids, "unpredictable" results are obtained. In accordance with the foregoing, the skilled artisan would conclude that "undue experimentation" is required to practice the claimed invention.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

*D. Lukton* 8/19/03

\*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

*Christopher Low*

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